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10/509,675	09/13/2006	Piero Del Soldato	026220-00055	3644

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ARENT FOX LLP
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
4173	

NOTIFICATION DATE	DELIVERY MODE
11/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,675	DEL SOLDATO, PIERO	
	Examiner	Art Unit	
	Jonathan S. Lau	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *2,5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 7-9* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is the national stage entry of PCT/EP03/03183, filed 27 Mar 2003; and claims benefit of foreign priority document ITALY MI2002A00077, filed 11 Apr 2002. Claims 1-9 are pending in the current application. Claims 2, 5 and 6, drawn to a nonelected species, are withdrawn. Claims 1, 3, 4 and 7-9 are examined on the merits herein.

Election/Restrictions

Applicant's amendment in the reply filed on 01 Nov 2007 is acknowledged. The newly amended claims are presently drawn to the invention of Group II and the Restriction Requirement has been rendered moot.

Applicant's election of species of the compound 2-fluoro-alpha-methyl[1,1'-biphenyl]-4-acetic acid 4-nitrooxy butylester (II^c) in the reply filed on 01 Nov 2007 is acknowledged.

Claims 2, 5 and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The disclosure is objected to because of the following informalities:

The instant specification is not arranged into sections with section headings as provided in 37 CFR 1.77(b) and recited above. It is unclear what text corresponds to the background of invention, for example.

The minor typographical error on page 2, line 13, "ialuronic".

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

The abstract of the disclosure is objected to because the phrase "the arthritis therapy" appears to refer to a specific arthritis therapy and it is unclear what this specific therapy is. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 4 is objected to because of the following informalities: in the generic structure of group IIb) on page 14 as drawn, the groups R_{2a} and R_{3a} appear to be bonded to the group R_{1a} instead of the C because of the formatting of the text. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the degenerative effects on cartilaginoid matrix, does not reasonably provide enablement for preventing degenerative effects on cartilaginoid matrix or relapses of degenerative effects on

cartilaginoid matrix. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: A method of preventing or reducing the degenerative effects on cartilaginoid matrix comprising administering to a subject with arthritis an effective amount of one or more compounds of the formula disclosed in instant claim 1 or salts thereof.

The state of the prior art: Prevent is defined as "keep from happening or arising; make impossible". See provided definition of prevent (definition of prevent, WordNet, cited in PTO-892). There is no prior art disclosing making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Armour et al. (Arthritis and Rheumatism, provided by applicant as reference AN in IDS filed 08 Oct 2004) discloses "Although traditional NSAIDs are widely prescribed for the treatment of inflammatory and degenerative disorders of the

musculoskeletal system, they do not appear to exert major protective effects on bone loss in humans." (page 2191, right column, lines 23-27) and "Previous work has shown that HCT1026 [flurbiprofen nitroxylbutylester] retains the antiinflammatory and analgesic properties of the nonnitrosylated parent compound, flurbiprofen, but is less likely to cause gastrointestinal side effects. We show here that HCT1026 has additional advantages over the parent NSAID, in that it exerts potent inhibitory effects on osteoclast formation and bone resorption in vitro and prevents ovariectomy-induced bone loss in vivo." (page 2192, left column, lines 1-9) However, the data of Armour et al. discloses only the reduction of bone loss, as illustrated by the graphs in Figure 6 on page 2190, showing a percent change due to bone loss that is significantly different from 0. Absolute prevention, or making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible, is not disclosed.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The lack of any prior art disclosing making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible means that one skilled in the art cannot predict the usefulness of a method to make degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Therefore the claimed invention is unpredictable.

The Breadth of the claims: The scope of the claims specifically includes prevention of making degenerative effects on cartilaginoid matrix (instant claims 1, 3, 4 and 7-9) or relapses of degenerative effects on cartilaginoid matrix (instant claim 9).

The amount of direction or guidance presented: The specification speaks generally about inhibition of TNFα-induced inflammatory changes. See instant specification, page 31, lines 21-25. No limiting definition of "prevention" that would preclude the definition recited above is given.

The presence or absence of working examples: The only working examples provided are for reduction of IL-6 release. For example, see instant specification, example F3, page 35 and results in table 3, spanning pages 42-42.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as preventing degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the invention with the full range of all possible treatment methods beyond those known in the art, (such as reducing the degenerative effects on cartilaginoid matrix) one skilled in the art would undertake a novel and extensive research program to show that the compounds of the formula disclosed in instant claim 1 made degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Because this research would have to be exhaustive, and because it would involve such a wide and unpredictable scope of compounds and disease-affected subjects, it would constitute an undue and unpredictable experimental burden.

> *Genentech*, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for **prevention** of degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Armour et al. (Arthritis and Rheumatism, provided by applicant as reference AN in IDS filed 08 Oct 2004).

Armour et al. discloses HTC1026 or flurbiprofen nitroxylbutylester (page 2185, left column, lines 10-11), the elected species, administered in vivo using a mouse model of ovariectomy-induced bone loss (page 2185, left column, lines 16-17) to inhibit bone resorption (page 2185, right column, lines 3-4). For the structure of flurbiprofen, see attached entry from The Merck Index (The Merck Index, cited in PTO-892). Armour et al. discloses flurbiprofen nitroxylbutylester may be used for treatment of arthritis, characterized by joint inflammation as well as periarticular and systemic bone loss (page 2185, right column, lines 8-12). The disclosure of flurbiprofen nitroxylbutylester administered to a mouse model of ovariectomy-induced bone loss, a subject with

arthritis, to inhibit bone resorption and treat periarticular and systemic bone loss, or reduce degenerative effects on the cartilaginoid matrix, anticipates instant claims 1, 3, 4, and 7. The phrase "degenerative effects on the cartilaginoid matrix" of instant claim 1 includes bone loss in a joint due to bone resorption. Armour et al. discloses administration of flurbiprofen nitroxylbutylester by intraperitoneal injections in corn oil (page 2186, right column, lines 7-9), anticipating parenteral administration disclosed in instant claim 8.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Ardin Marschel can be reached on 571-272-0718 or Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JSL

/Ardin H Marschel/
Supervisory Patent Examiner, Art Unit 1614